

Cumulative Risk to Thyroid Hormone Disruptors

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Environmental Issue:

Thyroid hormones are important factors in the development of the central nervous system and the reproductive system.

A broad range of structurally diverse chemicals decrease thyroid hormone concentrations in serum and tissues.

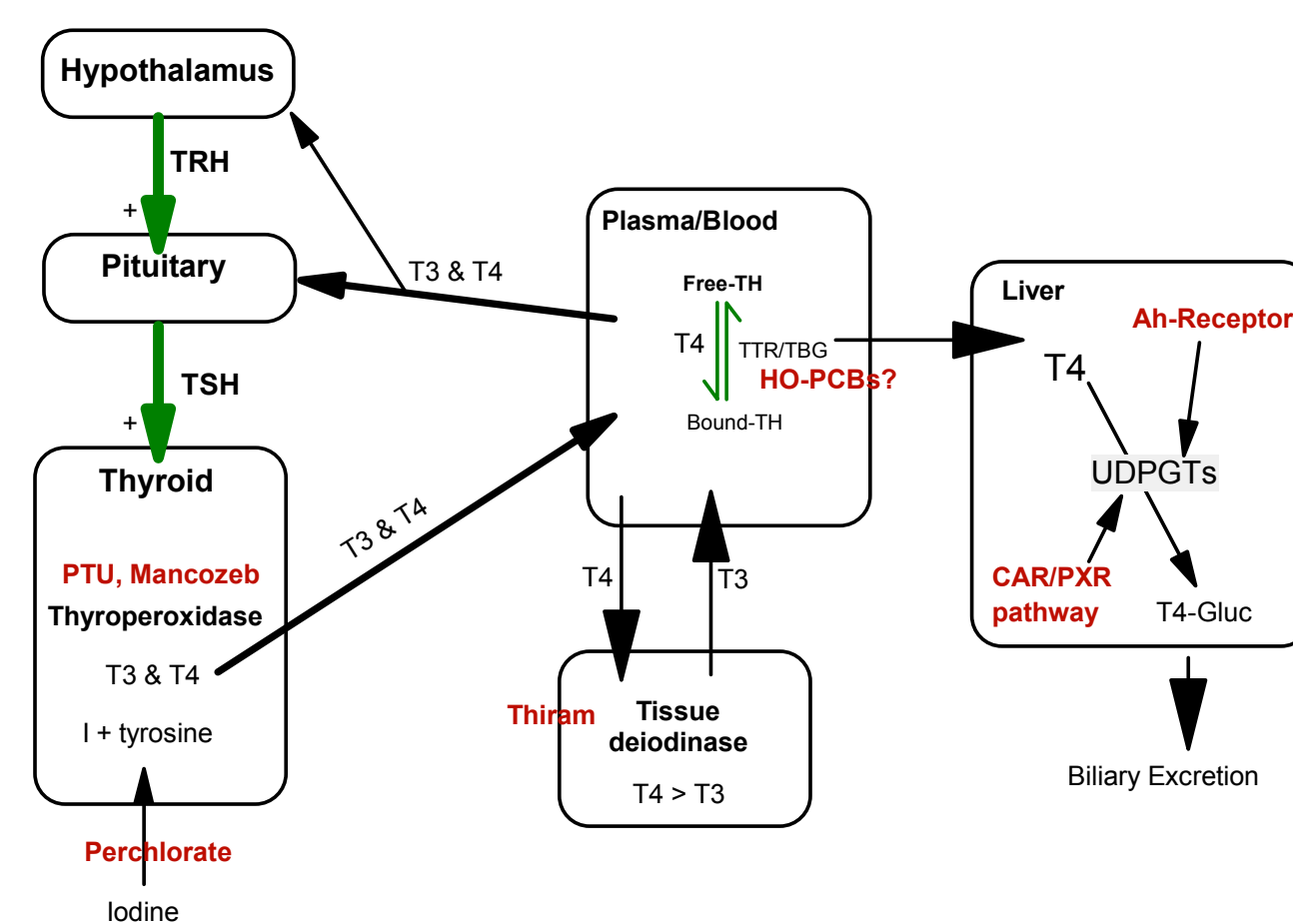
These chemicals act at multiple sites (modes of action) and through multiple mechanisms (molecular events) (See Fig 1).

Because of the importance of thyroid hormones during development, it would be valuable to understand the impact of exposures to multiple thyroid hormone disruptors.

Goal:

To examine the cumulative effects of chemicals that decrease thyroid hormones through different mechanisms of action and different modes of action.

Hypothalamus-Pituitary-Thyroid-Liver Axis



APPROACH

Chemicals:

Initially, we examined a series of PHAHs (dioxins dibenzofurans and PCBS). These induce UGTs through activation of the Ah receptor, PXR and/or CAR pathways.

Animals:

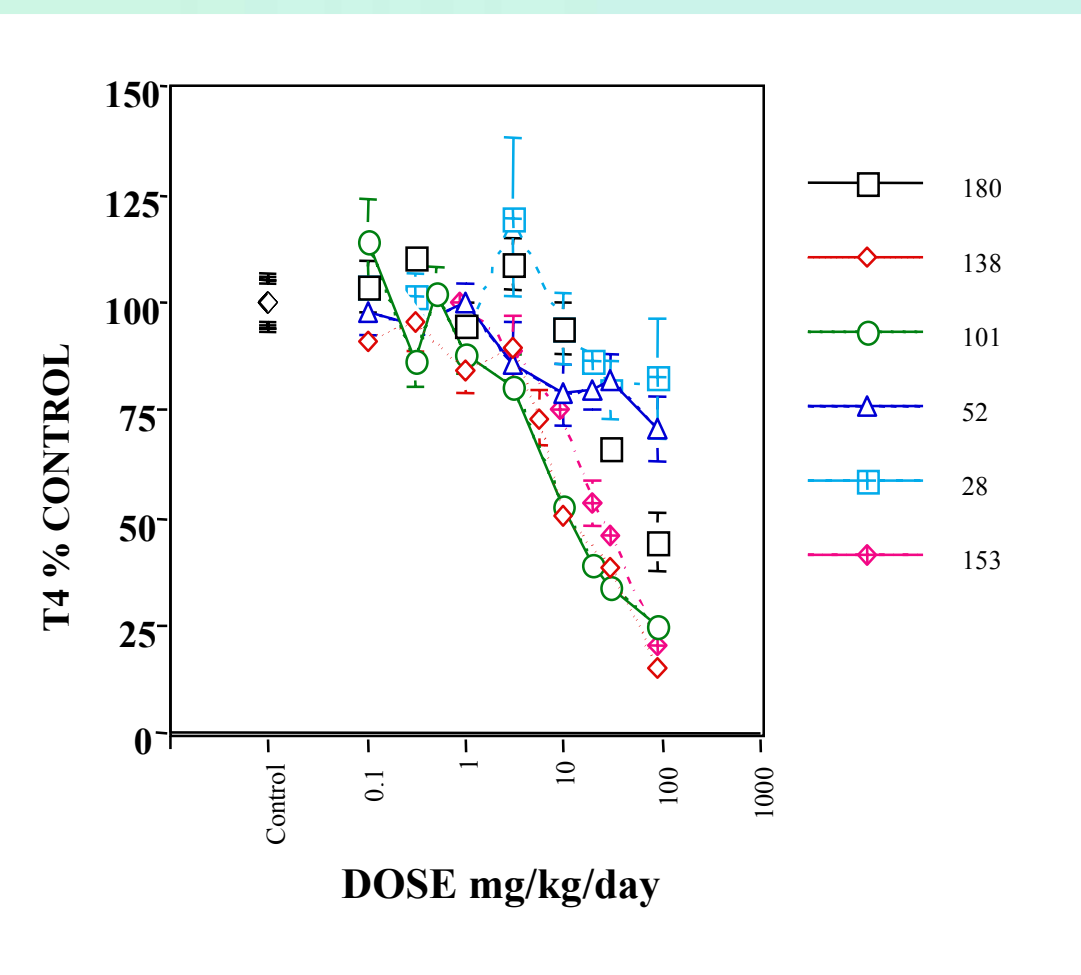
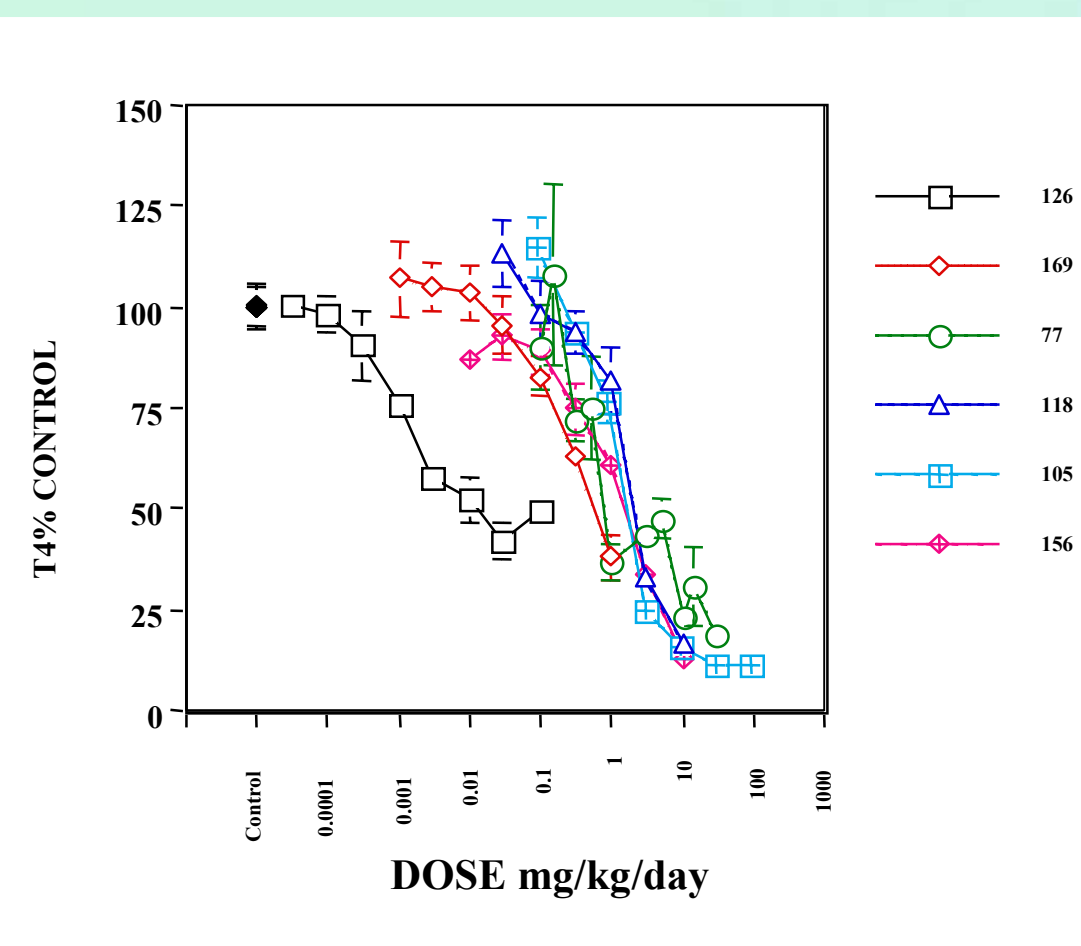
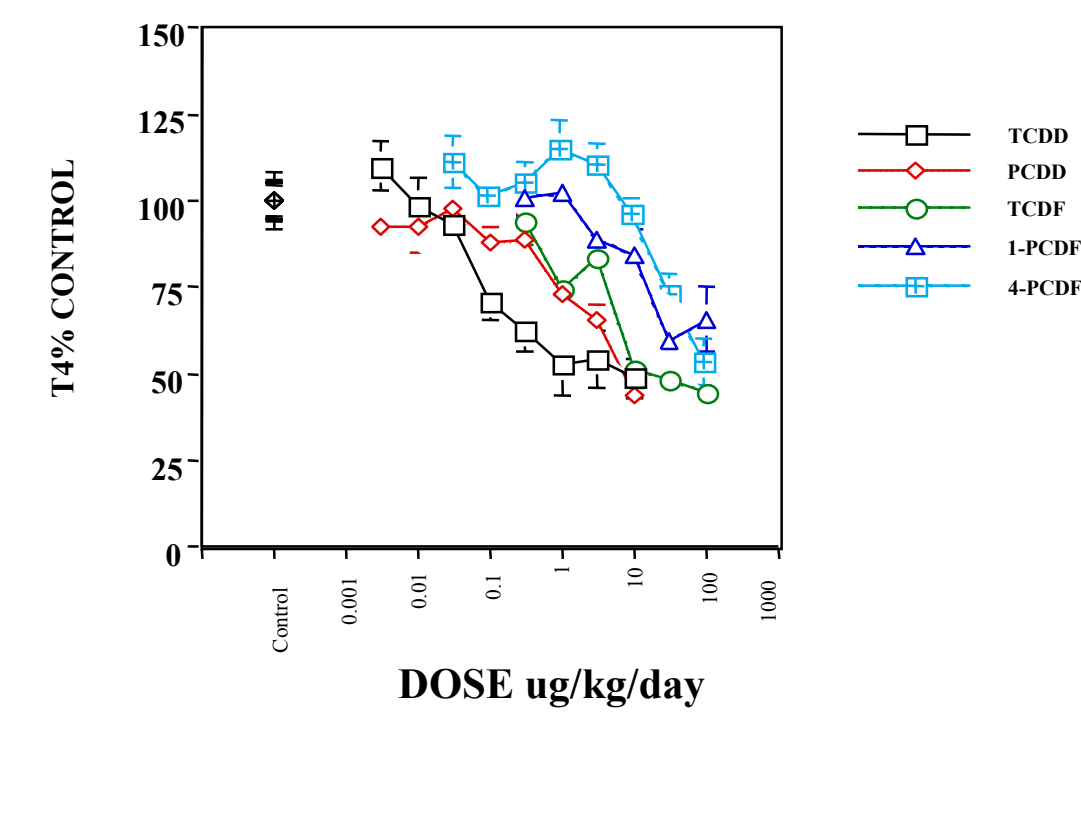
Female Long Evans rats 23 days old were obtained from Charles Rivers Laboratory. Rats were dosed by oral gavage for 4 consecutive days with either individual chemicals or a defined mixture and terminated 24 hrs after the last dose

T4 Assays: Serum thyroxine concentrations were determined using standard RIA commercial kits (Diagnostic Products Corp)

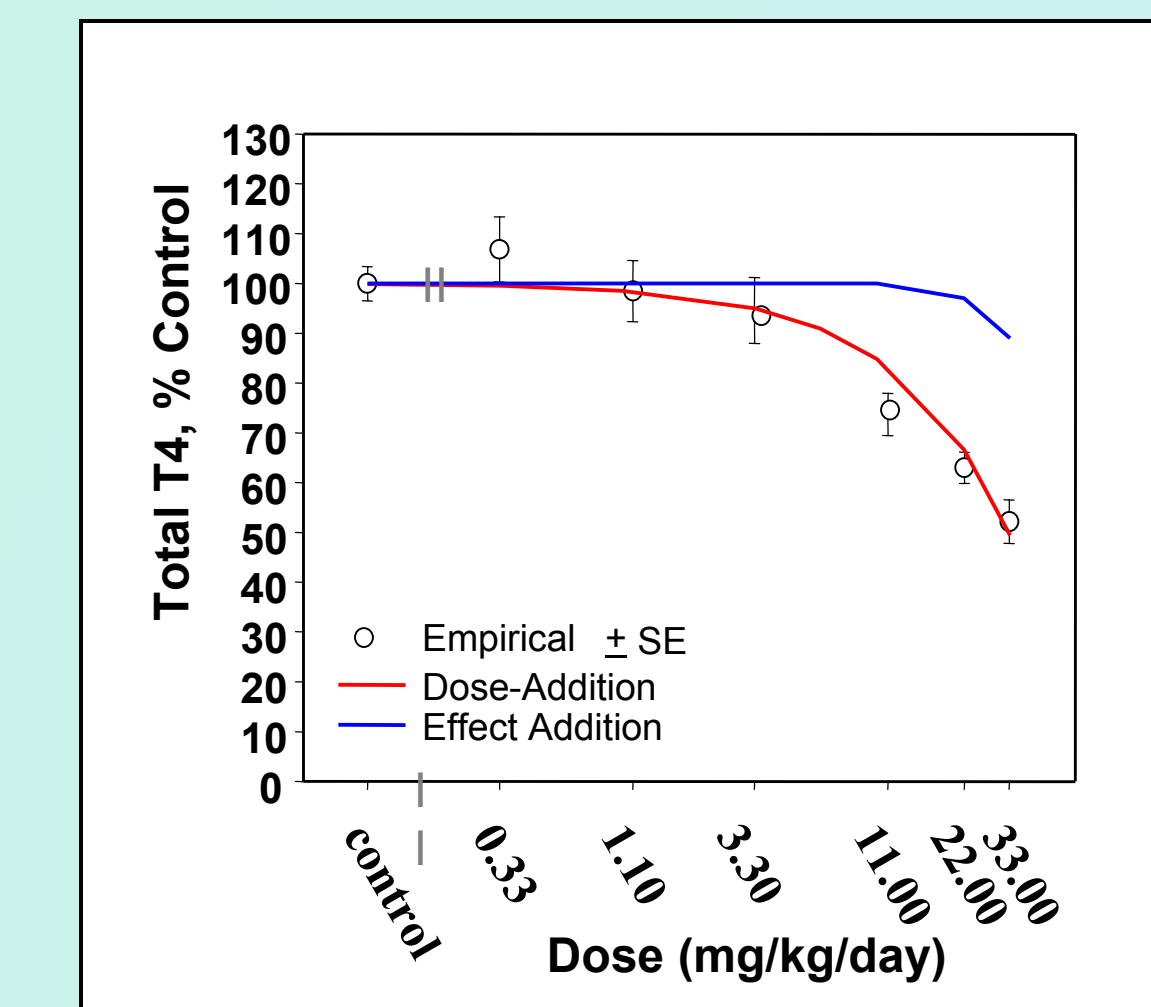
Statistics

A Hill model was fit to the data using Sigma-Stat and the dose that produced a 50% decrease was estimated.

The predicted response for the mixture was calculated in two methods. The first used a simple dose-addition theory (Gessner, 1988). The second used simple effect-addition theory.



Chemical	Daily Dose (ug/kg)	Relative to TCDD
TCDD	0.012914385	1.0
PCDD	0.012914385	1.0
TCDF	0.019371578	1.5
1-PCDF	0.006457193	0.5
4-Pcdf	0.02582877	2.0
OCDF	0.064571925	5.0
77	1.93715775	150
105	77.48631	6007
118	387.43155	30033
126	0.581147325	45
138	387.43155	30033
153	387.43155	30033
156	12.914385	1001
169	0.38743155	30
180	387.43155	30033



Conclusions

The PHAHs tested decreased serum thyroxine in rats.

The dose response relationships demonstrated different maximum effects and different slopes. This suggests that these chemicals act through different mechanisms of action and potentially different modes of action.

Using the dose response relationship for the individual chemicals, the effect of the mixture was reasonably well predicted using a dose addition assumption.

Effect addition significantly under predicted the response of the mixture.

Impact

The USEPA often uses an assumption of dose addition when assessing the effects of complex mixtures that induce the same toxicity. This data demonstrates that for chemicals that alter thyroid hormones the assumption of dose addition is valid at exposures well below the NOELs for the individual chemicals.

Future Directions

A number of other methods are available to examine dose addition. These methods will be used to test the robustness of the assumption of dose addition observed in this analysis.

These experiments suggest that chemicals that decrease thyroid hormones by inducing UGTs are dose additive in mixtures. Future studies will examine the dose addition assumption in mixtures that include chemicals that alter thyroid hormones through other modes of action.